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PRINCIPAL INVESTIGATOR: Shiv Pillai, M.B.B.S., Ph.D.

CONTRACTING ORGANIZATION: Massachusetts General Hospital
Boston, Massachussets 02114

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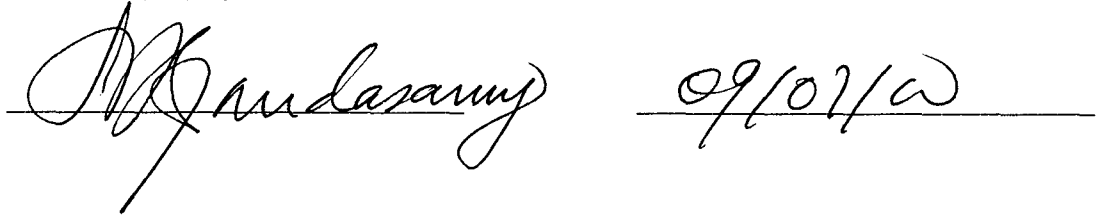

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13. ABSTRACT ***(Maximum 200 Words)***

Although human tumors of viral origin are clearly linked to HLA class II genes, few studies have examined whether breast cancer has an immunogenetic basis. MHC class II alleles can be very precisely typed using molecular approaches. Given that point mutations in oncogenes and tumor suppressor genes may contribute novel epitopes, and given the possibility that many tumors arise in areas of chronic inflammation, linkage of cancer to the MHC class II locus is clearly worth examining. We have typed all MHC class II alleles in 183 patients (all Caucasians under the age of 40) with breast cancer and 233 ethnically matched controls using a total of 133 different Single Stranded Oligonucleotide probes. While our analyses our ongoing, we have noted an extremely strong association (with a p value of <0.0001) of a specific DQB1 allele with breast cancer. This allele was detected in 1 out of 86 controls but was inherited by 74 out of 183 patients with breast cancer. We would like to stress the preliminary nature of this finding.

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Julio Pillai 9/10/99

PI - Signature Date

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INTRODUCTION

Although human tumors of viral origin are clearly linked to HLA class II genes, few studies have examined whether breast cancer has an immunogenetic basis. MHC class II alleles can be very precisely typed using molecular approaches. Given that point mutations in oncogenes and tumor suppressor genes may contribute novel epitopes, and given the possibility that many tumors arise in areas of chronic inflammation, linkage of cancer to the MHC class II locus is clearly worth examining. In this study we have used molecular approaches to type all HLA class II DP, DQ, and DR alleles in patients who were diagnosed with breast cancer before the age of 40, and in ethnically matched controls. The goal was to identify if any specific MHC class II allele is linked either positively or negatively in this disease.

BODY

We have typed all MHC class II alleles in 183 patients (all Caucasians under the age of 40) with breast cancer and 233 ethnically matched controls using a total of 133 different Single Stranded Oligonucleotide probes. While our analyses our ongoing, we have noted an extremely strong association (with a p value of <0.0001) of a specific DQB1 allele with breast cancer. This allele was detected in 1 out of 86 controls but was inherited by 74 out of 183 patients with breast cancer. We would like to stress the preliminary nature of this finding. Over the next few weeks when our analyses are complete, we will re-examine all autoradiographs and repeat assays with selected probes to verify whether this extremely striking preliminary result is correct.

While we typed (spotted PCR amplified products and probed separately with the above mentioned 133 probes) samples from 183 breast cancer patients and 233 controls, the analysis of this very large number of results is still in progress. In the accompanying Tables statistics have been performed on subsets of patients and controls which have been completely analyzed (Tables I and II). No significant differences in the frequencies of DPB1 alleles were noted in patients with breast cancer and controls (Table I-attached). Very significant differences were noted when DQB alleles were typed (Table II-attached). Apart from the very strong positive association seen in patients with breast cancer for DQB1* 0601 ($p< 0.0001$), significant negative associations were also noted with DQB1*03032 and DQB1*05031 ($p=0.0006$ for both). All available typing results for DQB1 and DRB1 are summarized in Tables III and IV (attached). We realize that our DQB findings in Table II may, if correct, prove extremely important both from a pathogenetic and therapeutic viewpoint. We therefore cannot stress enough the importance of considering this to be a preliminary finding until all films are reviewed and the data rechecked thoroughly.

We expect, that if our data is verified we will submit a paper on the analysis of all DQB and DPB alleles in breast cancer patients and controls by mid-October 1999. We believe it is premature to statistically analyze our existing DRB1 alleles until we have verified the assignment of alleles for all DRB1, DRB3, DRB4, and DRB5 alleles. All the

experimental work of typing has been completed but we expect all the DR related allele assignments to be completed and checked in about 6 weeks time, at which time a second manuscript will be prepared.

KEY RESEARCH ACCOMPLISHMENTS:

- Complete (but preliminary) molecular analyses of all MHC class II genes in patients with breast cancer and controls has been performed
- Extremely strong susceptibility and resistance DQB alleles have been identified in women with breast cancer, but results should still be considered preliminary.

REPORTABLE OUTCOMES

Two manuscripts are in preparation.

CONCLUSIONS

If our preliminary results are verified, we may conclude that there is an extremely significant immunogenetic component to breast cancer. This suggest that some form of inflammatory process may be critical for oncogeneis and leaves open the possibility that immune surveillance may be of critical importance in the genesis of breast cancer in young women. There are obvious and very important therapeutic implications which will be considered more fully if we are able to verify and fully establish our preliminary findings.

TABLE I: FREQUENCIES OF DPB1 ALLELES IN BREAST CANCER

DPB1 ALLELES	CONTROLS (n = 90)	PATIENTS (n = 94)	p Value
DPB1*0101	7.8% (7)	5.3 % (5)	0.5610
DPB1*0201	18.9% (17)	19.1 % (18)	1.0000
DPB1*0202	1.1% (1)	0.0% (0)	0.4891
DPB1*0301	20.0% (18)	15.9 % (15)	0.5652
DPB1*0401	50% (45)	62.7 % (59)	0.1018
DPB1*0402	30.0% (27)	33.0 % (31)	0.7513
DPB1*0501	0.0% (0)	0.0 % (0)	-------
DPB1*0601	2.2% (2)	3.2 % (3)	1.0000
DPB1*0801	1.1% (1)	1.1 % (1)	1.0000
DPB1*0901	0.0% (0)	1.1 % (1)	1.0000
DPB1*1001	7.8% (7)	6.4 % (6)	0.7790
DPB1*1101	2.2% (2)	3.2 % (3)	1.0000
DPB1*1301	4.4% (4)	2.1 % (2)	0.4367
DPB1*1401	4.4% (4)	4.2 % (4)	1.0000
DPB1*1501	3.3% (3)	1.1 % (1)	0.3602
DPB1*1601	0.0% (0)	0.0 % (0)	-------
DPB1* 1701	2.2% (2)	1.1 % (1)	0.6148

DPB1*1801	1.1% (1)	2.1 % (2)	1.0000
DPB1*1901	1.1% (1)	1.1 % (1)	1.0000
DPB1*2001	7.8% (7)	8.5 % (8)	1.0000
DPB1*2101	0.0% (0)	0.0 % (0)	-------
DPB1*2201	0.0% (0)	1.1 % (1)	1.0000
DPB1*2301	20.0% (18)	14.9 % (14)	0.4376
DPB1*2401	0.0% (0)	0.0 % (0)	-------
DPB1*2501	1.1% (1)	1.1 % (1)	1.0000
DPB1*2601	0.0% (0)	2.2 % (2)	-------
DPB1*2701	3.3% (3)	1.1 % (1)	0.3602
DPB1*2801	0.0% (0)	0.0 % (0)	-------
DPB1*2901	1.1% (1)	1.1 % (1)	1.0000
DPB1*3001	0.0% (0)	1.1 % (1)	1.0000
DPB1*3101	0.0% (0)	1.1 % (1)	1.0000
DPB1*3201	0.0% (0)	1.1 % (1)	1.0000
DPB1*3301	0.0% (0)	0.0 % (0)	--------
DPB1*3401	0.0% (0)	0.0 % (0)	-------
DPB1*3501	2.2% (2)	1.1 % (1)	-------
DPB1*3601	1.1% (1)	1.1 % (1)	1.0000

TABLE II: FREQUENCIES OF DQB1 ALLELES IN BREAST CANCER

DQB1 ALLELES	CONTROLS (n=86)	PATIENTS (n=183)	p Value
DQB1*0201	24.4% (21)	15.3% (28)	0.0898
DQB1*0301	46.5% (40)	27.8% (51)	0.0036*
DQB1*0302	19.8% (17)	19.1% (35)	1.0000
DQB1*03031	0.0% (0)	0.5 % (1)	1.0000
DQB1*03032	9.3% (8)	0.5 % (1)	0.0006**
DQB1*0401	0.0% (0)	2.7 % (5)	0.1806
DQB1*0402	4.7% (4)	1.6 % (3)	0.2150
DQB1*0501	18.6% (16)	19.7 % (36)	0.8703
DQB1*0502	4.7% (4)	0.5% (1)	0.0374
DQB1*05031	9.3% (8)	0.5% (1)	0.0006 **
DQB1*05032	0.0% (0)	1.6% (3)	0.5536
DQB1*0504	0.0% (0)	0.0% (0)	--------
DQB1*0601	1.2% (1)	40.4% (74)	<0.0001***
DQB1*0602	26.7% (23)	24.6 % (45)	0.7639
DQB1*0603	11.6% (10)	18.0 % (33)	0.2139
DQB1*0604	4.7% (4)	2.7% (5)	0.4732
DQB1*0605	0.0% (0)	6.6 % (12)	0.0206

TABLE III: DQB1 ALLELES IN INDIVIDUAL PATIENTS WITH BREAST CANCER

PATIENT	DQB1
1	*0603 *0301
2	*0302 *03032
3	*0301 *0603
4	*0602 *05032
5	*0603 *0501
6	*0501 *0601
8	*0302 *0601
9	*0501 *0201
10	*0302 *0602
11	*0601 *0401
12	*0602 *0302
13	*0301 *0602
15	*0602 *0501
16	*0201 *0302
17	*0501 *0601
18	*0402 *0201
19	*0501 *0601
20	*0603 *0605
21	*0402 *0601
24	*0501 *0601
27	*0501 *0601
30	*0605 *0302
31	*0501 *0601
32	*0501 *0601
34	*0601 *0301
36	*0603 *0605
37	*0201 *0302
39	*0302 *0201
41	*0602 *0603
42	*0601 *0301
44	*0603 *0602
45	*0602 *0302
46	*0601 *0501
47	*0401 *0601
48	*0601 *0502
52	*0605 *0302
54	*0602 *0302
55	*0301 *0601
56	*0201 *0601
57	*0605 *0501
58	*0601 *0501
60	*0501 *0401
61	*0601 *0301
63	*0601 *0302
64	*0302 *0601
65	*0601 *0605
66	*0201 *0302
68	*0302 *0602
69	*0501 *0601
70	*0601 *0301

PATIENT	DQB1
71	*0601 *0301
72	*0501 *0601
73	*0602 *0501
74	*0301 *0602
75	*0601 *0302
77	*0602 *0201
78	*0602 *0201
80	*0601 *0401
81	*0501 *05032
82	*0602 *0501
83	*0301 *0601
85	*0601 *0301
88	*0602 *0302
89	*0602 *0201
90	*0301 *0601
91	*0601 *0301
92	*0605 *0301
93	*0601 *0301
95	*0302 *0602
96	*0201 *0501
97	*0201 *0501
98	*0301 *0601
99	*0601 *0301
101	*0301 *0201
102	*0201 *0601
103	*0603 *0602
104	*0201 *0501
105	*0201 *0302
106	*0201 *05031
107	*0603 *0605
108	*0301 *0601
109	*0301 *0601
111	*0603 *0201
112	*0602 *0603
113	*0603 *0602
114	*0201 *0501
116	*0603 *0602
117	*0301 *0201
118	*0602 *0603
119	*0601 *0301
121	*0201 *03031
123	*0605 *0603
124	*0601 *0301
125	*0602 *0603
126	*0601 *0603
127	*0602 *0603
128	*0602 *0603
129	*0601 *0602
130	*0603 *0602
132	*0302 *0201
133	*0601 *0602
135	*0201 *0302

PATIENT	DQB1
136	*0201 *0302
137	*0601 *0501
138	*0601 *0301
139	*0302 *0602
140	*0602 *0302
265	*0601 *0301
266	*0601 *0301
270	*0501 *0601
275	*0501 *0601
276	*0401 *0402
277	*0601 *0301
279	*0201 *0302
281	*0301 *0601
283	*0601 *0603
284	*0601 *0301
285	*0301 *0601
286	*0301 *0302
287	*0603 *0302
288	*0604 *0603
289	*0301 *0302
290	*0602 *0603
292	*0601 *0201
293	*0603 *0501
294	*0301 *0601
295	*0602 *0603
297	*0604 *0501
298	*0302 *0201
299	*0501 *0601
300	*0602 *0501
301	*0601 *0301
302	*0602 *0501
303	*0601 *0301
305	*0301 *0601
306	*0301 *0601
307	*0601 *0301
308	*0501 *0604
332	*0604 *0602
334	*0603 *0602
335	*0501 *0201
337	*0201 *0302
338	*0501 *0601
339	*0601 *0501
340	*0501 *0503
341	*0601 *0301
346	*0301 *0601
347	*0601 *0301
349	*0501 *0602
350	*0201 *0302
351	*0301 *0302
353	*0301 *0601
354	*0501 *0601
355	*0602 *0603

PATIENT	DQB1
357	*0601 *0302
358	*0301 *0601
359	*0301 *0605
361	*0501 *0605
365	*0604 *0605
366	*0602 *0603
367	*0602 *0603
372	*0601 *0301
373	*0601 *0302
375	*0601 *0401
376	*0302 *0602
377	*0301 *0302
378	*0302 *0201
379	*0602 *0601
381	*0601 *0301
382	*0602 *0302
383	*0602 *0603
384	*0603 *0602
385	*0301 *0601
386	*0601 *05032
387	*0601 *0501
389	*0302 *0201
390	*0605 *0501
391	*0601 *0301
396	*0301 *0601
397	*0602 *0603

Table IV: DRB1 ALLELES OF INDIVIDUALS WITH BREAST CANCER

PATIENT	DRB1
1	*1302 *1102
2	*1405 *1302
3	*1405 *1305
4	*1601 *0102
5	*1302 *1405
6	*1405 *1104
8	*14 *08
9	*0701 *1405
10	*0701 *0405
11	*08
12	*0302 *15
13	*1501
15	*0103 *15
16	*0701 *0301
17	*0103 *0103
18	*0302
19	*0102 *1103
20	*0302 *1405
21	*1405 *0301
24	*0701 *0102
27	*0301 *1302
30	*1403
31	*0701 *1405
32	*0701 *1405
34	*0701 *1403
36	*1302 *1501
37	*0302
39	*0402 *0302
41	*1305 *1405
42	*07 *1403
44	
45	*1405 *0406
46	*0701 *1405
47	*0101 *07
48	*1302 *1405
52	*0401 *1302
54	*1501 *0401
55	*1501 *0401
56	*1303 *1303
57	*0102 *0302
58	*0102 *1301
60	*08 *1202
61	*04
63	*1302 *0302
64	*1405 *08
65	*0401 *1302
66	*0701 *03
68	*0401 *0302
69	*0701 *01
70	*0401 *14

PATIENT	DRB1
71	*0701 *1202
72	
73	*01
74	*1501 *0407
75	*04 *1602
77	*0302
78	
80	*08 *1408
81	*0101 *07
82	*01
83	*04 *0302
85	*0404 *1403
88	*07 *1503
89	*1502
90	*1403
91	*1405 *0302
92	*13 *03
93	*07 81403
95	*0405 *1302
96	*1405 *03
97	*0701
98	*1303
99	*1303
101	*0701 *0407
102	*0302 *1601
103	*0408 *1501
104	*0701 *0101
105	*0701 *04
106	*0407 *0302
107	*0701 *13
108	*1303
109	*07 *1403
111	*1503
112	*07 *1501
113	*13
114	*08
116	*03 *1305
117	*03 *13
118	*1501 *1302
119	*0404 *1403
121	*07
123	*0407 *1302
124	*0302
125	*0302 *0408
126	*1501 *0101
127	*14 *13
128	*0101 *1501
129	*1501 *0408
130	*14 *08
132	*0302
133	*1502 *1202
135	*0701 *1405

PATIENT	DRB1
136	*0701 *1405
137	*1401
138	*14 *08
139	*1501
140	*1501 *1202
265	*11 *14
266	*12 *09
270	*08 *12
275	*03 *13
276	*03 *14
277	*1102 *1405
279	*14 *03
281	*04 *14
283	*14 *08
284	*08 *1202
285	*0411 *14
286	*04 *14
287	*14 *13
288	*1405 *13
289	*08 *1101
290	*04 *1303
292	*0301 *0701
293	*0701 *1302
294	*0701 *1405
295	*0701 *1405
297	*0701 *1303
298	*0701 *04
299	*0101 *0301
300	*0101 *04
301	*0701 *1401
302	
303	*1405 *0301
305	*0301 *1305
306	*0302 *1402
307	*08 *1304
308	*1302 *0302
332	*1405 *1302
334	*0701 *08
335	*0301 *1302
337	*1405 *0301
338	*0411 *0111
339	*1305 *0102
340	*0701 *1405
341	*1202 *0302
346	*0701 *1405
347	*08 *1305
349	*0101
350	*0301 *1405
351	*0102 *1303
353	*1405 *1104
354	*0301 *13
355	

PATIENT	DRB1
357	*09
358	*0101 *1202
359	*1405 *1302
361	*0101 *0302
365	*1405 *1303
366	*
367	*0301 *1405
372	*0405 *08
373	*1405 *04
375	*08 *1405
376	*1303 *0403
377	*0302 *1202
378	*0701 *1401
379	*
381	*04 *1405
382	*04 *
383	*04 *1305
384	*0701 *1402
385	*1303 *0302
386	*1405 *0301
387	*0701 *1405
389	*0701 *0301
390	*1302 *0302
391	*04 *1405
396	*1405 *1302
397	*1405 *0302

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FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
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Reports to be Downgraded to Unlimited Distribution

ADB241560	ADB253628	ADB249654	ADB263448
ADB251657	ADB257757	ADB264967	ADB245021
ADB263525	ADB264736	ADB247697	ADB264544
ADB222448	ADB255427	ADB263453	ADB254454
ADB234468	ADB264757	ADB243646	
ADB249596	ADB232924	ADB263428	
ADB263270	ADB232927	ADB240500	
ADB231841	ADB245382	ADB253090	
ADB239007	ADB258158	ADB265236	
ADB263737	ADB264506	ADB264610	
ADB239263	ADB243027	ADB251613	
ADB251995	ADB233334	ADB237451	
ADB233106	ADB242926	ADB249671	
ADB262619	ADB262637	ADB262475	
ADB233111	ADB251649	ADB264579	
ADB240497	ADB264549	ADB244768	
ADB257618	ADB248354	ADB258553	
ADB240496	ADB258768	ADB244278	
ADB233747	ADB247842	ADB257305	
ADB240160	ADB264611	ADB245442	
ADB258646	ADB244931	ADB256780	
ADB264626	ADB263444	ADB264797	